## REMARKS

Applicants gratefully acknowledge the courtesy of a telephonic interview on April 25, 2007. During the interview, Examiner Rawlings, Minh-Quan K. Pham, and the inventor, Dr. Katherine Meyer Siegler, discussed the outstanding rejections. The Examiner agreed to considered the amendment to claim 1 filed herein. In addition, the Examiner agreed to consider secondary evidence showing that the present invention is non-obvious and evidence showing that molecules secreted by the cells are not necessarily detectable in the serum.

The Office Action dated February 28, 2007, has been fully considered. The present Amendment is intended to be a complete response thereto and to place the case in condition for allowance.

The specification has been amended to include the limitations recited by original claims 5 and 23, and to correct a minor spelling error.

Claims 1-93 are pending. Claims 6-10, 16-22, and 24-93 have been withdrawn as being drawn to a non-elected invention. Claim 1 has been amended to specifically relate back to the preamble of the claim. No new matter is added.

THE SPECIFICATION ARE PROPER

The specification stands objected to for failing to provide proper antecedent bases for the limitations recited in claim 5 and 23. Applicant has amended the specification to include those limitations. Specifically, the paragraph bridging pages 8-9 (paragraph [0033] of the published application) have been amended to include "protein array," as suggested by the Examiner. The paragraph bridging pages 6-7 (paragraph [0023] of the published application) have also been amended to include the step of "comparing the levels of MIF in the serum of the individual to the

MIF levels of prostate cancer patients." No new matter has been added as claims 5 and 23 are original claims. Therefore, the specification now contains proper antecedent bases for the claims. Accordingly, Applicant respectfully requests withdrawal of the objection.

THE CLAIMS ARE NOT INDEFINITE

Claims 1-5, 11-15, and 23 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner alleges that "claim 1 fails to recite a positive correlation step that clearly relates back to the objective of the invention, as recited in the preamble of the claim." Claim 1 has been amended to recite the step of "detecting or diagnosing prostate cancer where the serum MIF levels are greater than about 5 to about 10 ng/ml." This step clearly is a positive correlation step that relates to the objective of the invention, i.e. detecting or diagnosing prostate cancer. Accordingly, Applicant respectfully requests withdrawal of the rejection.

THE CLAIMS ARE NOT ANTICIPATED

Claims 1-3 and 11-13 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Zhang et al. (*Hepatobilizry Pancreat. Dis. Int.* 2002 Nov., 1(4):577-580). Claims 1-3 and 11-15 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Mitamura et al. (*Br. J. Ophthalmol.* 2000, 84:636-639). Claims 1, 2, 4, and 11-13 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Leech et al. (*Arthritis Rheumatol.* 2000 Apr., 43(4):827-833) as evidenced by Mitamura et al. Applicant respectfully traverses the rejections.

To anticipate a claim under 35 U.S.C. § 102, the reference must teach every element of the claim. See MPEP § 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."

*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

Neither Zhang et al., Mitamura et al., nor Leech et al. disclose every element of the claimed invention. In particular, none of the references disclose a method for detecting or diagnosing prostate cancer. Zhang et al. discloses MIF in patients with chronic virus hepatitis B and hepatitis cirrhosis. Mitamura et al. discloses MIF in the vitreous of patients with proliferative diabetic retinopathy. Leech et al. discloses the regulation of MIF in rat adjuvant-induced arthritis. Although these are unfortunate diseases, they have no relation to prostate cancer, nor has the Examiner linked any of these diseases to prostate cancer. The present invention is drawn to a method of detecting or diagnosing prostate cancer. This is not disclosed in either Zhang et al., Mitamura et al., or Leech et al.

In the Final Office Action, the Examiner alleges that the claim "merely describes a 'result' that is achievable by practicing the process steps recited in the body of the claim, but *does not limit* the claimed process." Final Office Action, pages 6-7 and 8 (emphasis original). Applicant respectfully submits that the present amendment contains a positive step that limits the claims to detecting or diagnosing prostate cancer. This positive step cannot be interpreted as "merely describing a 'result.'" As such, neither Zhang et al., Mitamura et al., nor Leech et al. disclose a step of "detecting or diagnosing prostate cancer where the serum MIF levels are greater than about 5 to about 10 ng/ml" as recited by claim 1. Therefore, these references cannot

anticipate the present invention under the meaning of 35 U.S.C. § 102. Accordingly, Applicant respectfully requests withdrawal of the rejections.

THE CLAIMS ARE NOT OBVIOUS

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 103(a) as being obvious over Mitamura et al. in view of Leech et al. (*Arthritis Rheumatol.* 2000 Apr., 43(4):827-833). Claims 1, 2, and 5 stand rejected under 35 U.S.C. § 103(a) as being obvious over Mitamura et al. in view of Wright et al. (*Prostate Cancer Prostatic Dis.* 1999 Dec., 2(5/6):264-276). Claims 1-4, 11-13, and 23 stand rejected under 35 U.S.C. § 103(a) as being obvious over Hudson et al. (U.S. Patent No. 6,043,044) in view of Koong et al. (*Cancer Res.* 2000 Feb. 15, 60:883-887) and Meyer-Siegler (*J. Interferon Cytokine Res.* 2000, 20:769-778). Claims 1-4, 11-13, and 23 stand rejected under 35 U.S.C. § 103(a) as being obvious over Hudson et al. in view of Koong et al., Meyer-Siegler, and Arcuri et al., as evidenced by Meyer-Siegler et al. (BCM Cancer. 2005 Jul 6; 5(1):73). Applicant respectfully traverses the rejections.

With regard to Mitamura et al. in view of Leech et al., both references, as discussed above, fail to disclose a method for detecting or diagnosing prostate cancer. Their combination still does not cure this deficiency. Therefore, because Mitamura et al. in view of Leech et al does not teach or suggest all the claim limitations, the references cannot render the present invention obvious within the meaning of 35 U.S.C. § 103.

With regard to Mitamura et al. in view of Wright et al., the deficiency of Mitamura et al. is disclosed above. The Examiner relies on Wright to teach "measuring the levels of serum biomarkers using a protein array." However, because this teaching does not cure the deficiency of Mitamura et al., and does not disclose any utility with respect to prostate cancer, combining

the references still fails to teach or suggest all the claim limitations, namely a method to detect or diagnose prostate cancer.

With regard to the obviousness rejections over Hudson as combined with Koong et al., and Meyer-Siegler (2000); or with Koong et al., Meyer-Siegler (2000), and Arcuri et al.; the combination of references does not render the invention obvious for several independent reasons. First, the references, taken alone or in combination, fail to teach or suggest all the claim limitations. In particular, the references fail to disclose "detecting or diagnosing prostate cancer where the serum MIF levels are greater than about 5 to about 10 ng/ml" as recited in claim 1. None of the cited references teach the presence of prostate cancer where the MIF serum levels are greater than about 5 to about 10 ng/ml, except Meyer-Siegler et al. (2005) which is not prior art as it is published after the filing date of the present invention.

Second, from the teaching of the cited references, it is not obvious that MIF is detectable in the serum. Hudson et al. teach detection of prostate cancer by measuring MIF in the prostate tissue. Meyer-Siegler (2000) disclose that prostate cells secrete MIF in cell culture, not *in vitro*. Koong et al. disclose that PAI-1 is over expressed in cancer cells and is detectable in blood serum. From this information, the Examiner alleges that the present invention would have been obvious to one of ordinary skill in the art. Particularly, the Examiner alleges Koong et al. teach that "a tumor antigen, such as MIF, is over expressed and secreted by cancer cells, its presence in the serum of subject's [*sic*] afflicted by the disease is readily determined." This allegation is erroneous. Koong et al. merely teach that PAI-1 is detectable in blood serum. With regard to MIF, Koong et al. merely disclose that it is one of the hypoxia induced genes, but fail to mention or perform detection of MIF in the serum. Of the nine genes mentioned (*PAI-1*, *IGFBP-3*, *LRP*, *BIK*, *MIF*, *MMP-13*, *FGF-3*, *GADD45*, and *VEGF*), only the translation product of *PAI-1* was

detected in the serum by Koong et al. None of the other proteins are mentioned as being found in the serum. Therefore, from this disclosure, the Examiner's general conclusion that a secreted cancer antigen can be found in the serum is erroneous and cannot be found in the teaching of Koong et al.

Moreover, although Siegler et al. (2000) discloses the secretion of MIF by prostate cell culture, there is no teaching that these cells secrete MIF *in vivo*. The cell culture was grown and maintained in an artificial environment to induce secretion of MIF. This artificial environment does not approximate or mimic actual prostate cell conditions *in vivo*. Therefore, the extrapolation of these artificial conditions to actual *in vivo* conditions is tenuous at best. Additionally, even if Siegler et al. (2000) show that the prostate cells are likely to secrete MIF *in vivo*, which Applicant disputes, there is no reasonable expectation that the secreted MIF will show up in the serum.

To provide for the deficiency of Siegler et al. (2000), the Examiner relies on Arcuri et al. to show that MIF is secreted into the prostatic fluid. Even so, there are a multitude of biological processes that may prevent MIF from showing up in the serum, which include being taken up by other cells or being degraded before ever reaching the serum.

Applicant respectfully submits herewith 1) Borgono et al. (*Cancer Res.* 2003, Dec. 15, 64:9032-9041) which discusses human kallilkrein 14 (KLK14) and its role in prostate cancer (*see* Introduction; and Results, page 9037, left column; and 2) Li et al. (*Cancer Epimediology, Biomarkers & Prevention* 2005, June, 14(6):1557-1561) which discusses vascular endothelial growth factor (VEGF) and its role in prostate cancer (*see* Abstract; Introduction; and page 1560, left column, last paragraph). According to these references, both KLK14 and VEGF are normally both secreted by the prostate, can be found in normal serum, and are overexpressed in

prostate cancer patients. However, neither protein can be found in increased concentrations in the serum of prostate cancer patients. This clearly shows that an increase in expression and secretion of a protein by a cell is not readily detectable in the serum, and contradicts the Examiner's assertion that "because Koong et al. teaches since a tumor antigen, such as MIF, is overexpressed and secreted by cancer cells, its presence in the serum of subject's afflicted by the disease is readily determined." Final Office Action, page 17. Therefore, even if a molecule is overexpressed and secreted by the cells in a disease state, the detection of the increased level in the serum is not at all obvious.

Third, secondary considerations showing that others were skeptical of the invention points away from obviousness. *See* MPEP 2141(III) (Skepticism of experts and failure of others are secondary evidence to be considered in determining obviousness); MPEP 716.05 ("Expressions of disbelief by experts constitute strong evidence of non-obviousness." (emphasis added)). Applicant respectfully submits herewith Michael et al. (*Cancer Epidemiology*, Biomarkers & Prevention 2004, February, 13:328-329) and Michael et al. (*The Prostate* 2005, 62:34-39). Both references express skepticism of the present invention, as published in Meyer-Siegler et al. (2002), and present evidence that serum MIF is not a valid biomarker for prostate cancer. Michael et al., however, fail to appreciated that serum MIF indicates prostate cancer only where "the serum MIF levels are greater than about 5 to about 10 ng/ml," as claimed in the present invention. It is clear from reviewing the data presented in the Michael et al. references that the MIF levels they looked at are all much below 5 ng/ml. *See* Michael et al. (2004), Table 1; and Michael et al. (2005), page 36, left column. Thus, the disbelief of Michael et al. in MIF as a marker for prostate cancer and their failure to comprehend the criticality of the range of

"greater than about 5 to about 10 ng/ml" clearly points to the non-obviousness of the present invention.

Therefore, for the reasons noted above, the present invention is not obvious over Hudson et al., Koong et al., Meyer-Siegler (2000), and Arcuri et al., taken alone or in combination. Accordingly, Applicant respectfully requests withdrawal of the rejection.

CONCLUSION

Applicant has responded to the Office Action mailed February 28, 2007. A Request for Continued Examination and fee therefor are filed herewith. All pending claims are now believed to be allowable and favorable action is respectfully requested.

In the event that there are any questions relating to this Amendment or to the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that the prosecution of this application may be expedited.

Please charge any shortage or credit any overpayment of fees to BLANK ROME LLP, Deposit Account No. 23-2185 (111828-00109). In the event that a petition for an extension of time is required to be submitted herewith and in the event that a separate petition does not accompany this response, Applicant hereby petitions under 37 C.F.R. 1.136(a) for an extension of time.

Any fees due are authorized above.

Respectfully submitted,

Date: 5/21/07

Charles R. Wolfe, Jr.
Registration No. 28,680

BLANK ROME LLP

Watergate
600 New Hampshire Avenue NW
Washington, DC 20037
Telephone: (202) 772-5800
Facsimile: (202) 772-5858